



Kinetics of Oxidation of Etamsylate by Chloramine-B in Alkaline Medium- A Mechanistic Approach

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ABSTRACT

The kinetics of oxidation of etamsylate (ETM) by N-chlorobenzenesulphonamide (CAB) in NaOH medium has been investigated at 303K. The reaction rate shows a first order dependence on $[CAB]_0$ and fractional order with respect to both $[ETM]_0$ and $[OH^-]_0$. Effects of added benzenesulphonamide and halide ions have been investigated. The effect of dielectric constant of the medium by varying $[MeOH]$ shows an inverse effect. The variation of ionic strength of the medium has no significant effect on the rate of the reaction. The reaction fails to initiate polymerization of acrylamide. The Michaelis – Menten type of kinetics has been proposed. The reaction was studied at different temperatures and the values of thermodynamic parameters were computed. The reaction stoichiometry and oxidation products have been identified and a suitable mechanism has been proposed.

Keywords : Kinetics, Oxidation, Chloramine-B, Etamsylate, Alkaline Medium.

INTRODUCTION

Etamsylate (ETM), chemically known as 2,5-dihydroxybenzenesulphonic acid; N-ethylethanamine has haemostatic properties. ETM stops haemorrhage from small blood vessels by stabilizing the capillary wall and correcting abnormal platelet adhesion and is prescribed for the management of blood loss in menorrhagia and after surgery[1].

N-haloamines are mild oxidants and generally undergo a two electron change per mole in its reactions. They act as sources of halonium cations, hypohalite species and N-anions, which act both as bases and nucleophiles[2]. There are many reports on N-halocompounds behaving as oxidizing agents[3-6]. However, a review of literature shows that there are few reports on chloramines-B (CAB) as an oxidizing agent[7-9].

Literature survey shows that there is no information available on the kinetics and oxidation of etamsylate by CAB from the mechanistic view point. There was a need for understanding the mechanism of oxidation of this drug, so that this study may throw some light on the metabolic conversions in the biological system. Therefore, in the present communication, we report the kinetics and mechanism of oxidation of etamsylate by chloramine-B in NaOH medium 303K .

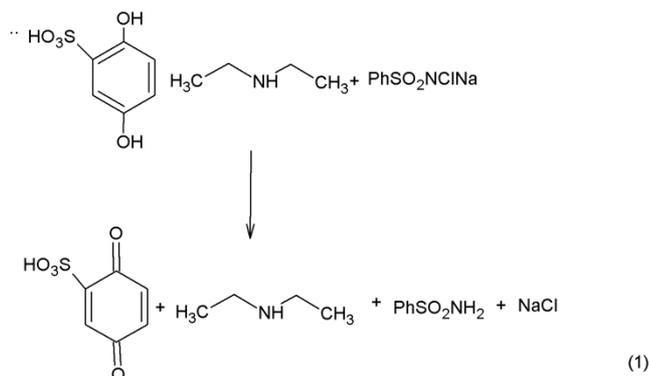
EXPERIMENTAL SECTION

An aqueous solution of CAB was prepared[10], standardized iodometrically and stored in brown bottles to prevent any photochemical deterioration. The substrate etamsylate (Biocon Ltd) was used as received. The aqueous solution of the substrate was prepared freshly each time. All the other chemicals used were of analytical grade. Doubly distilled water was used for all the measurements.

The reactions were carried out under pseudo- first order conditions by keeping an excess of etamsylate over CAB. Solutions containing appropriate amounts of ETM, NaOH and water (to keep the total volume constant for all runs) were taken in a glass-stoppered pyrex boiling tube, and thermostated at 303K. A measured amount of CAB solution, also thermostated at the same temperature, was rapidly added to the mixture. The progress of the reaction was monitored by iodometric estimation of unreacted CAB in a measured aliquot (5ml) of the mixture at different time intervals. The course of the reaction was studied up to 75 to 80% completion. The pseudo- first order rate constants (k') evaluated from the plots of $\log[\text{CAB}]$ versus time, were reproducible within $\pm 4\%$.

Stoichiometry and Product Analysis

Reaction mixtures containing varying proportions of CAB and etamsylate in the presence of NaOH were equilibrated at 303K for 24h. Estimation of unreacted CAB showed that one mole of etamsylate consumed one mole of oxidant.



The reduction product of oxidant, benzenesulphonamide (BSA) was detected [11] by thin layer chromatography using petroleum ether, chloroform and 1- butanol (2:2:1v/v/v) as the solvent and iodine as the detecting agent ($R_f = 0.88$). It was further confirmed by its melting point $150\text{-}151^\circ\text{C}$ (reported m.p. = $149\text{-}152^\circ\text{C}$). One of the product N-ethylethanamine was detected by spot tests [12] and the major product 3,6-dioxo cyclohexa-1,4-diene-1-sulphonic acid was detected by spot tests and IR spectroscopy which shows a strong peak at 1345cm^{-1} , 1668cm^{-1} and 1702cm^{-1} .

RESULTS AND DISCUSSION

Effect of varying reactant concentrations on the reaction rate

The oxidation of ETM by CAB was kinetically investigated at different initial concentrations of reactants in NaOH medium at 303K. Under pseudo-first order conditions, with the substrate in excess, at constant $[\text{ETM}]$, $[\text{NaOH}]$ and temperature, plots of $\log [\text{CAB}]_0$ versus time were linear, indicating a first order dependence of the reaction rate on $[\text{CAB}]_0$. Under identical experimental conditions, an increase in $[\text{ETM}]_0$ leads to an increase in the k' values (Table 1). A plot of $\log k'$ versus $\log [\text{ETM}]_0$ was linear with a slope of 0.53 (Fig.1) showing a fractional order dependence of the rate on $[\text{ETM}]_0$.

Table 1: Effect of varying concentrations of the reactants

$10^4[\text{CAB}]$ (mol dm ⁻³)	$10^3[\text{ETM}]$ (mol dm ⁻³)	$10^3[\text{NaOH}]$ (mol dm ⁻³)	$10^4 k'$ (s ⁻¹)
10.0	5.0	5.0	2.46
10.0	10.0	5.0	3.57
10.0	20.0	5.0	5.20
10.0	50.0	5.0	8.50
5.0	10.0	5.0	3.54
10.0	10.0	5.0	3.57
15.0	10.0	5.0	3.47
20.0	10.0	5.0	3.59
10.0	10.0	2.0	1.78
10.0	10.0	5.0	3.57
10.0	10.0	10.0	6.35
10.0	10.0	15.0	9.01

$I = 5.0 \times 10^{-3} \text{ mol dm}^{-3}$; $T = 303\text{K}$

Effect of varying [OH⁻] and [Cl⁻] on the reaction rate

The rate of the reaction increased with increase in [NaOH]. A plot of $\log k'$ versus [NaOH] was linear with a fractional slope of 0.80 (Table 1, Fig.2) indicating a fractional order dependence on [OH⁻]. At constant [OH⁻], addition of Cl⁻ in the form of NaCl had no significant effect on the rate of the reaction.

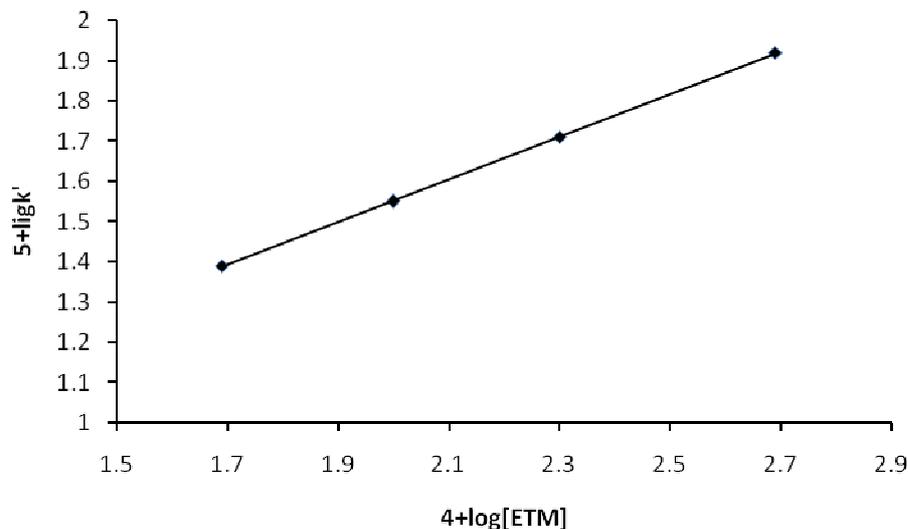


Fig 1: Effect of [ETM] on the reaction rate

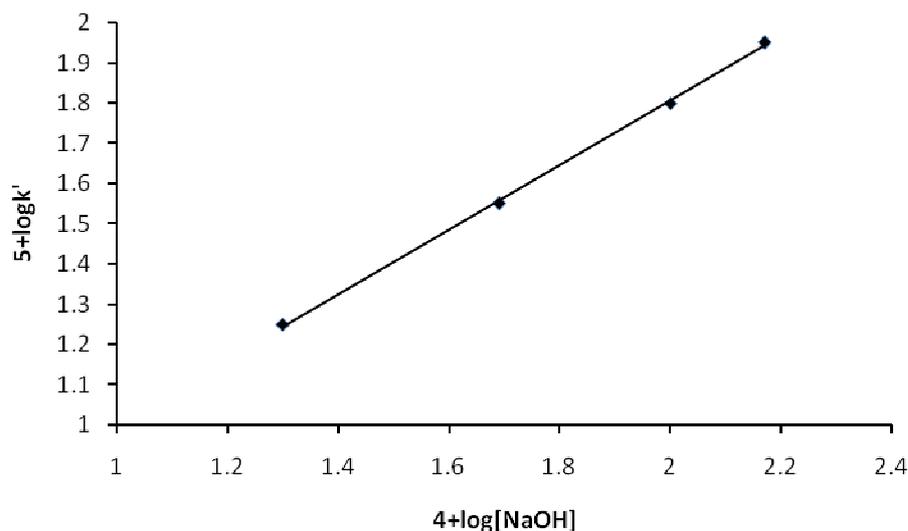


Fig 2: Effect of [NaOH] on the reaction rate

Effect of added benzenesulphonamide on the reaction rate

The addition of reduction product of CAB, benzenesulphonamide (BSA or PhSO₂NH₂) had no effect on the rate of the reaction.

Effect of dielectric permittivity of the medium and varying ionic strength on the reaction rate

The dielectric permittivity of the medium was varied by adding different proportions of methanol to the reaction mixture. The rate of the reaction decreased with increase in methanol content (0- 40% v/v). A plot of $\log k'$ versus $1/D$, where D is the dielectric permittivity of the medium (D values taken from the literature [13]) gave a straight line with a negative slope of 0.64 (Table 2). Blank experiments with methanol however showed that there was slight decomposition of the solvent under the given experimental conditions. Variation of ionic strength of the medium had a negligible effect on the rate of the reaction.

Table 2 : Effect of varying dielectric constant of the medium

[MeOH] (%v/v)	$10^2/D$	$10^4 k'$ (s^{-1})
0.0	1.30	3.57
10.0	1.38	3.24
20.0	1.48	2.82
30.0	1.60	2.30

$$[CAB] = 1.0 \times 10^{-3} \text{ mol dm}^{-3}; [ETM] = 10.0 \times 10^{-3} \text{ mol dm}^{-3}; I = 5.0 \times 10^{-3} \text{ mol dm}^{-3}; [NaOH] = 5.0 \times 10^{-3} \text{ mol dm}^{-3};$$

$$T = 303K$$

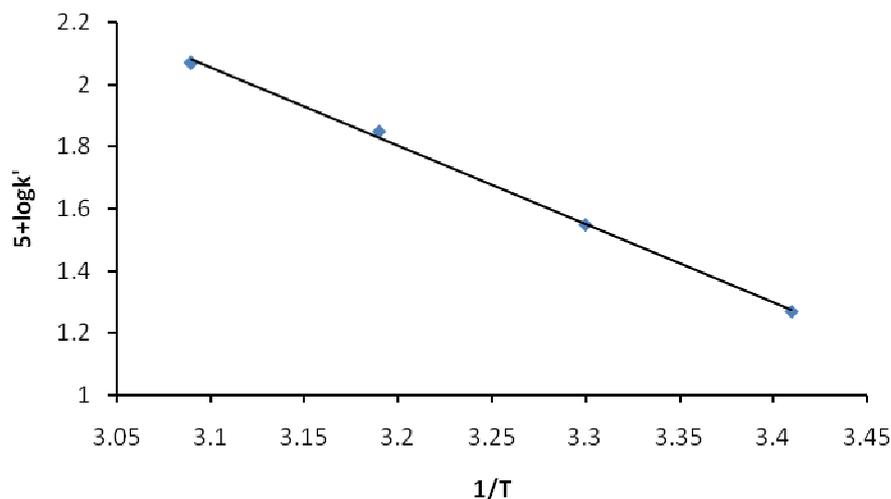
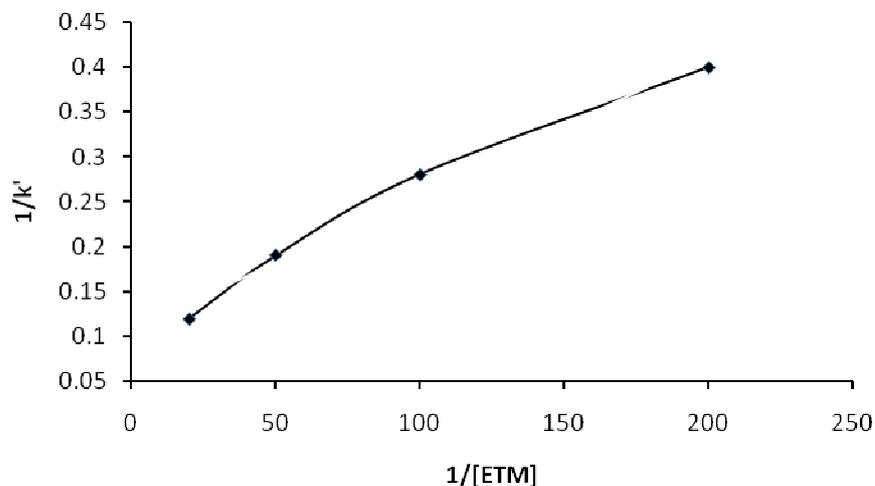
Effect of varying temperature on the reaction rate.

The reaction was studied at different temperatures (Table 3) and from the linear Arrhenius plot of $\log k'$ versus $1/T$, (Fig.3) values of activation parameters have been computed.

Table 3 : Effect of varying temperature and activation parameters

Temperature (K)	$10^4 k'$ (s^{-1})	Activation Parameters	
		Parameter	Value
293	1.87 (4.48)	E_a (kJ mol^{-1})	48.34 (39.97)
303	3.57 (9.43)	ΔH^\ddagger (kJ mol^{-1})	45.77 (37.40)
313	7.08 (11.2)	ΔS^\ddagger ($\text{J K}^{-1} \text{ mol}^{-1}$)	-171.10 (-145.47)
323	11.80 (23.40)	ΔG^\ddagger (kJ mol^{-1})	56.42(81.48)

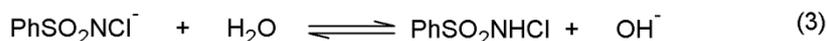
Values in parenthesis are the decomposition constants and activation parameters for the rate determining step.

**Fig 3 : Effect of temperature on the reaction rate.****Fig 4 : Double reciprocal plot of $1/[ETM]$ versus $1/k'$**

Test for free radicals

Addition of the reaction mixtures to acrylamide did not initiate polymerization which indicates the absence of free radical species in the reaction sequence.

Chloramine-B is analogous to chloramine-T and behaves as a strong electrolyte in aqueous solutions[14,15], forming different species as shown in equation 2-6.

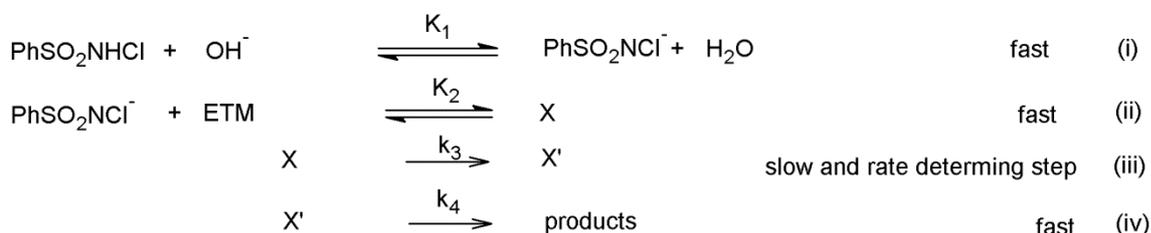


The probable oxidizing species in alkaline medium are PhSO_2NHCl , $\text{PhSO}_2\text{NCl}^-$ and HOCl .

Hardy and Johnston[16] have reported the following equilibria in alkaline solutions of CAB.

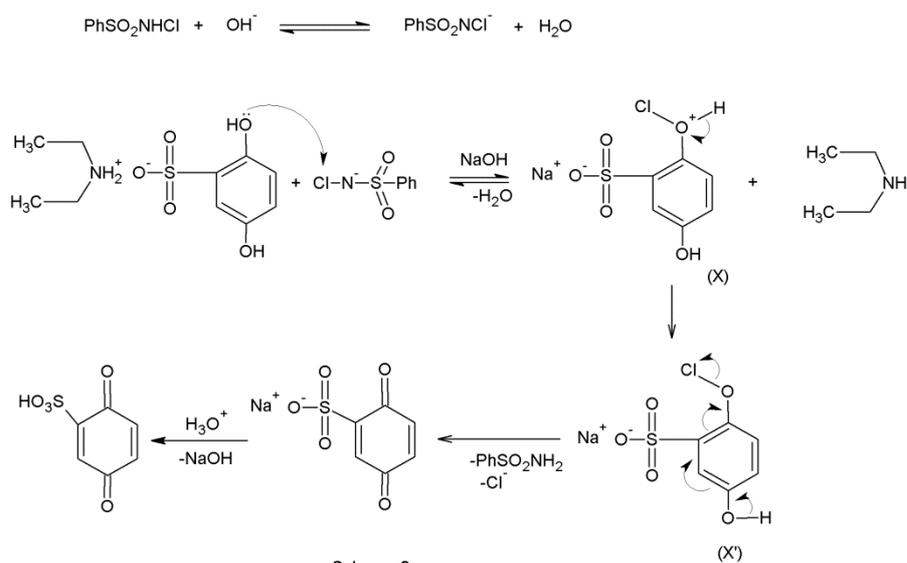


As equation 8 indicates a slow hydrolysis, if HOCl is the primary oxidizing species, a first order retardation of rate by the added benzenesulphonamide would be expected which is contrary to the experimental results. If PhSO_2NHCl were to be the oxidizing species, a retardation of the rate by $[\text{OH}^-]$ would be expected, which was not observed. In the present investigations, the rate of the reaction is accelerated by $[\text{OH}^-]$ ions. Therefore it is likely that the anion $\text{PhSO}_2\text{NCl}^-$ itself acts as the reactive species. Hence, the following mechanism (Scheme 1) is proposed to account for the observed kinetics:



Scheme 1

A detailed mechanistic interpretation of oxidation of etamsylate by CAB in alkaline medium and the structure of the intermediates are depicted in Scheme 2. An initial equilibrium involves the formation of the active oxidizing species of CAB, $\text{PhSO}_2\text{NCl}^-$. In the next step, the reactive oxidizing species attacks the substrate to form complex cation (X). In the slow and rate determining step, the complex cation forms complex intermediate species (X'). This complex decomposes to form the product.



Scheme 2

If $[\text{CAB}]_t$ represents the total effective concentration of CAB, from Scheme 1

$$[\text{CAB}]_t = [\text{PhSO}_2\text{NHCl}] + [\text{PhSO}_2\text{NCl}^-] + [\text{X}] \quad (9)$$

From steps (i) & (ii) of Scheme 1, the value of [X] obtained is,

$$[\text{X}] = \frac{[\text{CAB}]_t K_1 K_2 [\text{ETM}] [\text{OH}^-]}{[\text{H}_2\text{O}] + K_1 [\text{OH}^-] \{1 + K_2 [\text{ETM}]\}} \quad (10)$$

From slow step (step (iii)) of Scheme 1,

$$\text{rate} = k_3 [\text{X}] \quad (11)$$

By substituting the value of [X] from equation (10) into equation (11), we get

$$\text{rate} = \frac{K_1 K_2 k_3 [\text{CAB}]_t [\text{ETM}] [\text{OH}^-]}{[\text{H}_2\text{O}] + K_1 [\text{OH}^-] \{1 + K_2 [\text{ETM}]\}} \quad (12)$$

Above rate law (equation 12) is in good agreement with the experimental results wherein a first order dependence of rate on $[\text{CAB}]_0$ and fractional order on both $[\text{ETM}]_0$ and $[\text{OH}^-]$ was observed.

Since, $\text{rate} = k' [\text{CAB}]_t$, rate law (equation 12) can be transformed into equations (13)- (14)

$$k' = \frac{K_1 K_2 k_3 [\text{ETM}] [\text{OH}^-]}{[\text{H}_2\text{O}] + K_1 [\text{OH}^-] \{1 + K_2 [\text{ETM}]\}} \quad (13)$$

$$1/k' = \frac{1}{K_2 k_3 [\text{ETM}]} \left\{ \frac{[\text{H}_2\text{O}]}{K_1 [\text{OH}^-]} + 1 \right\} + \frac{1}{k_3} \quad (14)$$

From the intercepts of double reciprocal plots of $1/k'$ versus $1/[\text{ETM}]_0$ (Fig. 4), the values of decomposition constants k_3 were calculated using equation 14. The decomposition constant k_3 was found to be $9.43 \times 10^{-4} \text{s}^{-1}$ at 303K. Since the rate was fractional order in $[\text{ETM}]_0$, Michaelis-Menten type of kinetics [17] was adopted to study the effect of $[\text{ETM}]_0$ on the rate at different temperatures by plotting $1/k'$ versus $1/[\text{ETM}]_0$. Using the calculated k_3 values, activation parameters for the rate determining step were computed from the linear Arrhenius plot of $\log k_3$ versus $1/T$. These data are presented in Table 3.

A change in the solvent composition by varying the methanol content in methanol-water affects the reaction rate. The effect of varying solvent composition on the reaction kinetics has been described in several publications [18,19] for the limiting case of zero angle of approach between two dipoles or an ion-dipole system. Amis [19] has shown that a plot of $\log k'$ versus $1/D$ gave a straight line with a negative slope for a reaction between a negative ion and a

dipole or between two dipoles, while a positive slope indicates a reaction between a positive ion and a dipole. The negative dielectric effect observed in the present studies clearly supports the ion-dipole interaction in the rate limiting step.

The addition of halide ions had no effect on the rate indicating that no interhalogen or free chlorine was formed. The reaction product benzenesulphonamide does not influence the rate, showing that it is not involved in a pre-equilibrium. Variation of the ionic strength of the medium does not alter the rate indicating that non-ionic species are involved in the rate determining step.

The proposed mechanism is also supported by the moderate values of energy of activation. The fairly high positive values of ΔH^\ddagger and ΔG^\ddagger indicate that the transition state is highly solvated, while the high negative value of ΔS^\ddagger , suggests that the transition state is fairly rigid with less degree of freedom.

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